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APPLICATION OF ELECTROSPINNING TECHNIQUES FOR THE PRODUCTION OF TISSUE ENGINEERING SCAFFOLDS: A REVIEW

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Abstract

Electrospinning of nanofibers with diameters that fall into nanometer range have attracted growing attention in recent years due to the ability to produce scaffolds with nanoscale properties. Scaffolds from nanofibers for tissue engineering are large field. The goal of this review is to demonstrate an objective and overall picture of current research work on electrospinning technique, where different types of polymers are used for producing tissue engineering scaffolds. The target is also to describe the theory of different electrospinning process and discussing the applications and impacts of electrospinning on the field of tissue engineering.

Keywords: Electrospinning, Tissue Engineering, Nanofiber, Scaffold

Introduction

The nonwoven industry generally considers nanofibers as ‘having a diameter of less than one micron, although the National Science Foundation (NSF) defines nanofibers as having at least one dimension of 100 nanometer (nm) or less.

Nanofibers are the new class of materials, which are used for several value added applications such as medical textile, personal care, filtration, barrier, composite, insulation and energy storage. Due to the special properties of nanofibers they are suitable for a wide range of applications from medical to consumer products and industrial to high-tech applications for aerospace, energy storage, fuel cells, information technology, drug

delivery system and most importantly in the field of tissue engineering (Raghavendra R H et al. 2005).

Tissue engineering combines the design principles of living organisms and modern engineering with the development of viable substitutes of human tissues such as muscle, skin, cartilage, bone, even cardiovascular and neuronal structures. The field is developed via scaffolds implementing with a variety of bioactive molecules to balance cell proliferation and differentiation. Scaffolds are usually produced for the following purposes:

- To provide cell attachment, proliferation and migration
- To assist in the growth of three-dimensional tissue and organs
- Deliver and retain cells and biochemical factors
- Enable diffusion of vital cell nutrients
- Exert certain mechanical and biological influences to modify the behavior of the cell phase.

Tissue engineering scaffolds

Tissue engineering scaffolds are defined as three-dimensional structures that assist in the tissue engineering process by providing a site for cells to attach, proliferate, differentiate and secrete an extra-cellular matrix, eventually leading to tissue formation. It is also possible to guide cells into forming a neo-tissue of predetermined three-dimensional shape and size by optimizing the scaffold structure to get the desired cellular activities. Tissue engineering scaffolds can be either permanent or temporary in nature, depending on the application and the function of the neo-tissue. Usually temporary scaffolds are made from biodegradable polymers, such as polyglycolic acid, which degrade within the body to leave a purely biological neo-tissue (Freed, LE. et al, 1994). On the other hand, Permanent scaffolds remain within the body, working with ingrown tissue to form a polymeric/biological composite (Matsumoto H et al., 2001).

Electrospinning for tissue engineering application

Electrospinning is a simple and cost-effective method to produce scaffolds with an inter-connected pore structure and fiber diameters in the sub-micron range compared to self-assembly and phase separation techniques. The field of tissue engineering is thought to capitalize upon these features for the production of 2D or 3D scaffolds.

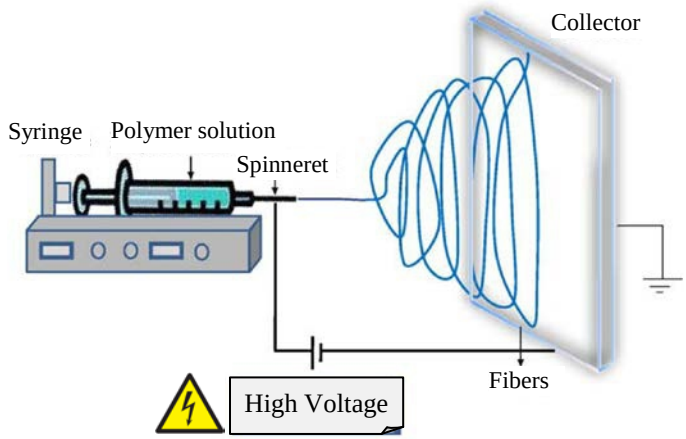

Fig.1: Schematic diagram of an electrospinning process (Nandana et al. 2010)

Three basic components as shown in figure 1 are required to setup the electrospinning process: a syringe with a metal spinneret of small diameters, a high voltage supplier and a rotating collector. A high voltage in the range of 10-50 kV is applied to create an electrically charged jet of polymer solution or melt out of the spinneret in the electrospinning process. A cone-shaped of the polymer solution droplet directed to the counter electrode is formed under the high voltage (Deitzel JM et al. 2001, Reneker DH et al. 2007). The droplet on the spinneret is slowly stretched as the voltage increasing and if the increase of voltage is continued, a jet is formed from the deformed droplet, which moves towards the counter electrode and becomes narrower in the process as in figure 2 (Theron SA et al. 2005). It is thought that the electrospinning gives us the impression of being a very simple and easily controlled technique for the production of nanofibers. But, actually the process is very intricate. That's why, it is also described as the interaction of several physical instability processes (Reneker DH et al. 2002, Theron SA et al. 2004). Advancement of this technique in both micro and nano fabrication have powered the field of tissue engineering in many aspect. More than 100 raw materials can be used in this technique.

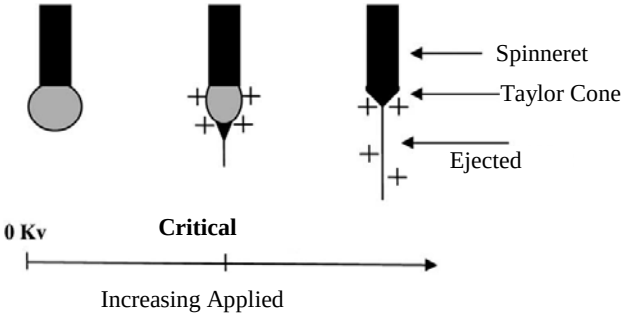

Fig.2: Schematic diagram of a taylor cone formation with increase in applied voltages (Wang HS et al. 2009)

Electrospinning of functional polymeric nanofibers and their application
Natural polymer scaffold

Most of the research on electrospinning of natural polymers is focused on biopolymers, because these naturally occurring polymers normally exhibit better biocompatibility and low toxicity than other polymers. Complicated solvent systems are usually required for electrospinning of natural biopolymers, such as hexafluoroisopropyl alcohol for collagen (Matthews JA et al. 2002, Rho KS et al. 2006) or gelatin (Li M et al. 2005) and formic acid for silk fibroin (Min BM et al. 2004, Wang H et al. 2005). Nmethylmorpholine (NMO)/water or N, N-dimethyl acetamide mixed solvent is used for electrospinning of cellulose (Kulpinski P et al. 2005, Kim CW et al. 2005). The silk fibroin is biocompatible and its powder is useful as a substance for growing or activating epidermal cells. Silk fibroin nanofiber mat from electrospinning is effective in regeneration of damaged periodical tissues and the correspondent membrane could guide bone tissue regeneration (Chung C.P et al. 2006).

Chitosan is a copolymer of N-acetyl-glucosamine and N-glucosamine units. It is produced by deacetylation of naturally occurring chitin, which is extracted from shellfish sources. The term chitosan is used when the percentage of N-acetyl-glucosamine units is lower than 50% (Jayakumar, R et al. 2008). Chitosan is accessible for various established processing technologies (e.g. freeze-drying, freeze-gelation) and has been used to produce films, gels as well as porous sponge-like scaffolds, because of its solubility in dilute acids. Chitosan has become a frequently applied material as regenerative medicine and biomaterials research including orthopedics, periodontology, drug delivery systems, wound healing applications and tissue engineering since last two decades (Manjubala, I et al. 2008, Hsu S. H et al. 2004).

Collagen is the most abundant protein family in the body, which has been extensively used for in vitro and in vivo tissue engineering. In many popular tissues, polymers of type I and type III collagen are the principal structural elements of the extracellular matrix (Parry and Craig, 1988). There are various types of collagens, which can be isolated from a variety of sources. More than 80% of collagens in the body consist of mainly type I, II & III and share similar features in all species. Collagen is highly conserved, relatively non-immunogenic and has been used in a variety of tissue engineering applications (Matthews JA et al. 2002). The function of collagen is to provide structural support to the tissue, in which it is present and at the same time it is also known to sequester many factors required for tissue regeneratopm amd maintenance. Therefore, it is also considered as ‘ideal’ scaffold material in the tissue engineering field (Boland ER et al. 2004). The classification of a solvent, which dissolved collagen at sufficient

concentrations to accomplish electrospinning and the volatile nature of the solvent for rapid drying of electrospun mats are the key issues for electrospinning of collagen. For the first time electrospinning of collagen is attempted by using type I collagen (calf skin) dissolved in hexafluro-2-propanol (HFP**)** and characterization with scanning electron microscopy (SEM) and transmission electron microscopy (TEM) is carried out. The electrospun collagen scaffolds have been applied for wound dressings and preliminary vascular tissue engineering as it provides an in vitro method to create a preformed, nanofibrous collagen scaffold that closely mimics the native collagen network (Matthews et al. 2003, Boland et al., 2004; Shields et al., 2004; Rho et al., 2006).

Synthetic homopolymer scaffold

Polycaprolactone (PCL) and polylactide (PLA) are biocompatible and biodegradable polymers, which can be synthesized by living ring-opening polymerization. They have been firstly electrospun into nanofibers as scaffolds in tissue engineering due to their biomedical properties (Bognitzki M et al. 2007, Chen F.J et al. 2006). The shape-ability and fiber surface morphology is difficult to design to fulfill the mechanical shapes and sizes, though electrospinning can be carried out easily.

Synthetic polymer scaffold

For modifying functional polymer materials, electrospun of block copolymers are of great interest. It is also possible to generate new materials of desired properties. The performance of electrospun fiber mat based on copolymers can be significantly improved in comparison with that of homopolymers, if the materials are properly implemented. For example, a biopolymer namely PLGA (copolymer of PGA and PLA) is popular and well-studied system that has been broadly used as electrospun scaffolds for biomedical applications. The mechanical properties and degradation of produced fiber is quite different from the original i.e. Polyglycolic acid (PGA**)** and PLA homopolymers. The nanofibrous PGLA scaffolds generally degrade faster than the regular casting film with the same dimensions and composition, mainly because of the nanofiber surface properties and the high water adsorption ability of the material (Zong X et al. 2002). Another example for biomedicine application is copolymer of P(LA-CL), which is synthesized from the copolymerization of Lactide and caprolactone. The degradation and properties of the copolymer is between those of the two homopolymers (PLA and PCL). The functionality and potential use of produced P(LA-CL) has been investigated by several groups (Kwon IK et al 2005, Mo XM et al. 2004, Xu CY et al. 2003). Other functional nanofibers are manufactured by electrospinning of environmental responsive copolymers, such as pH- responsive copolymer, thermal-responsive

copolymer etc. For example, the gel of a monodisperse triblock copolymer consisting of poly (methyl methacrylate-blockpoly [2-(diethylamino) ethyl methacrylate]-block-polymethyl methacrylate) has been shown pH-responsive behavior (Topham PD et al. 2006).

Synthetic extracellular matrices

One of the main objects of tissue engineering is to develop the design of polymeric scaffold with specific mechanical and biological properties similar to native extracellular matrix (ECM) in order to modulate cellular behavior (Langer R et al. 1993). A vast majority of the cells are in contact with the ECM in vivo, which is composed of a network of nano-meter-sized proteins and glycosaminoglycans. The intricate complexities of this spatial and temporal environment dynamically influence phenotypic and other cellular behavior by providing indirect and direct informational signaling cues (Xu, C et al. 2004). For example, the presence of an organized collagen type I ECM for integral binding is required for the development of osteoprogenitor cells towards mature osteoblasts in case of bone (Behonick D.J et al. 2003). The interactions between cells and ECM can modulate cellular activities such as migration, proliferation, differentiation and secretion of various hormones and growth factors (Franceschi R.T et al. 1992). Thus, the more closely the in vivo environment (i.e. chemical composition, morphology, surface functional groups) can be recreated, the success is more for the tissue engineering scaffold (Lan C.W et al. 2003). Tissue engineering scaffolds work as temporary ECMs until repair or regeneration occurs (Li W.J et al. 2002, Mo X.M et al. 2004 and Smith L.A et al. 2004).

Composite scaffolds

Electrospinning can also be used to produce composite scaffolds. For example, a scaffold with layers can be created by sequentially spinning different polymer solutions. Each layer can be tailored for specific cell adhesion and could be potentially beneficial for zonal articular cartilage or arterial vessel repair (Kidoaki S et al. 2005). Boland et al. have showed smooth muscle cell infiltration into a multi-layered scaffold of collagen types I and III and elastin, when cultured in a rotary cell culture system. Alternatively, two or more polymer solutions can be spun concurrently, resulting in a scaffold with mixed types of fibers (Boland, E.D et al. 2004). Collagen types I and III could be spun in this manner to create a scaffold better mimics their in vivo ratios.

Techniques used for electrospinning

Coaxial electrospinning

It has been investigated that nanofibers required the functionalizing agents (for example, biomolecules, such as enzymes, proteins, drugs, viruses and bacteria) for keeping them in the fluid environment to maintain their functionality. In order to meet their requirement, core-shell nanofibers are manufactured by a modified electrospinning process, such as coaxial electrospinning. Figure 3 shows the basic setup for coaxial electrospinning and the fabrication process of common core-shell nanofibers. Depending on the setup of electrospinning, two syringes feed inter-separated and coaxial 'inner fluid' and 'outer fluid' to spinneret. The electrospinning liquid is drawn out from spinneret and forms a 'compound taylor cone' with a core-shell structure under the application of high voltage (Loscertales, et al. 2002).

If the appropriate technical parameters are selected, core-shell nanofibers can be produced with high precision from a huge variety of materials by coaxial electrospinning process. Han et al. 2008 patented recently the composite nanofiber with a polycarbonate (PC) shell and a polyurethane (PU) core. The nonwoven fabric or membrane with the composite fiber combines the filtration efficiency of the PC with the mechanical characteristics, such as elasticity of PU. The membrane or fabric is useful in filters and aviation dresses or clothing. Extraordinary fiber structures could be formed through coaxial electrospinning of special polymers, such as the 'nanocables' can be formed with electrically conductive polyhexylthiophene as the core and Polyethylene oxide (PEO**)** as the insulating shell (Sun Z et al. 2003).

Coaxial electrospinning is not limited to the production of core-shell nanofibers with a continuous core. Core-shell droplet can also be generated by coaxial electrospinning. A coaxial jet of hydrophilic polymer (outside) and a hydrophobic liquid (inner) is electrospun, which produces beaded fibers, encapsulating the hydrophobic liquid into these beads (Díaz JE et al. 2006)

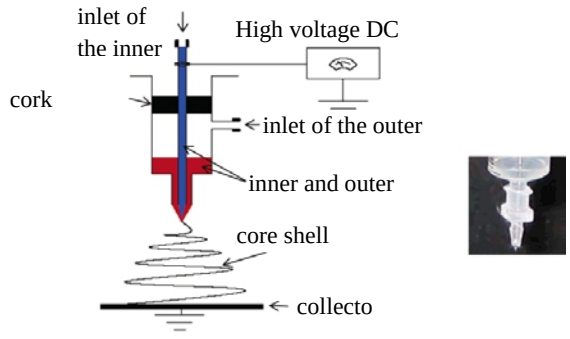

Fig.3: The basic setup for coaxial electrospinning (Zhang Y et al. 2004)

In this case, the beads are regularly distributed along the fibers and their sizes exhibit a uniformly distribution. The outer liquid flow rate control the bead to bead distance and fiber diameter, while the bead diameter can be maintained by controlling the inner liquid flow rate. Under the appropriate condition, it is possible to produce hollow fibers via coaxial electrospinning (Xia Y et al. 2006). Depending on evaporation of the solvent, the core polymer precipitates on the wall of the previously formed shell. Hollow nanofibers with functionalized inner and outer surfaces are directly fabricated by coaxial electrospinning (Li D et al. 2005). Now, it is thought that this technique provides a unique protocol for manufacturing complex catalyst system, drug delivery and filtration.

Modified electrospinning processes

Electrospinning procedure is further modified to accommodate the needs of materials for biomedical applications. Dual syringe reactive electrospinning as shown in figure 4 is one of such modifications (Ji J et al. 2006). The cross-linking reaction occurs simultaneously during the electrospinning process using a dual syringe mixing technique.

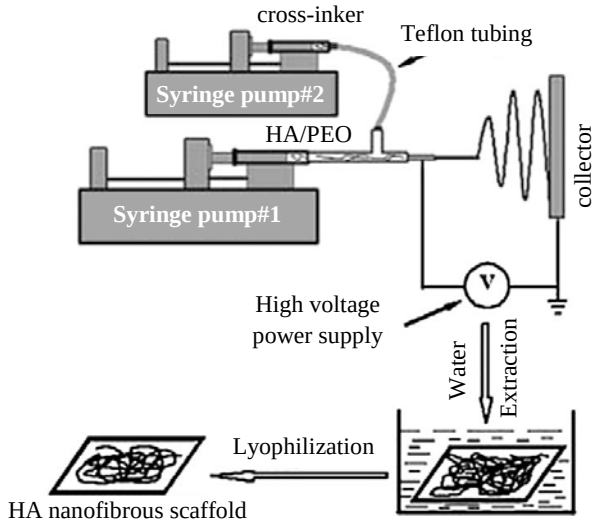

Fig.4: Schematic illustration of a modified electrospinning setup (Ji J et al. 2006)

Zhong et al. 2006 describes the fabrication of alligned collagen nanofibrous scaffolds. The electrospinning apparatus used by them is shown in figure 5. The structure and in vitro properties of these scaffolds are compared with a random collagen scaffold.

Highly porous 3D nanofibrous scaffold using PCL is made by electrospinning with the help of auxilliary electrode and chemical blowing agent (BA) by Kim et al. 2007.

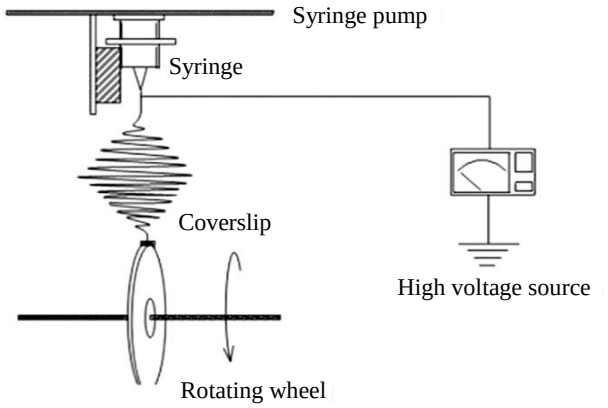

Fig.5: Fiber alignment during electrospinning (Agarwal et al. 2008)

Multi-channel coaxial electrospinning

The experimental setup of multi-fluidic compound-jet electrospinning is shown in figure 6. Various metallic capillaries with varying outer diameter and inner diameter are arranged at the several vertexes of an equilateral triangle. Then the bundle of capillaries is inserted into a plastic with gaps between individual inner capillaries and outer syringe. Two immiscible viscous liquids are fed separately to the three inner capillaries and outer syringe in an appropriate flow rate. A 20% Polyvinylpyrrolidone (PVP) ethanol solution is used as outer liquid, while a nondissolution paraffin oil is selected as inner liquid. Then a high voltage between three inner metallic capillaries and a metallic plate coated with a piece of aluminum foil acted as counter electrode and provide the driving and controlling for the electrospinning. The immiscible inner and outer fluids (red for paraffin oil and blue for $Ti(OiPr)_4$ solution) are carried out separately from individual capillaries. With the appropriate high voltage application, a whipping compound fluid jet is formed under the spinneret and then a fibrous membrane is collected on the aluminium foil (Fengyu Li et al. 2010).

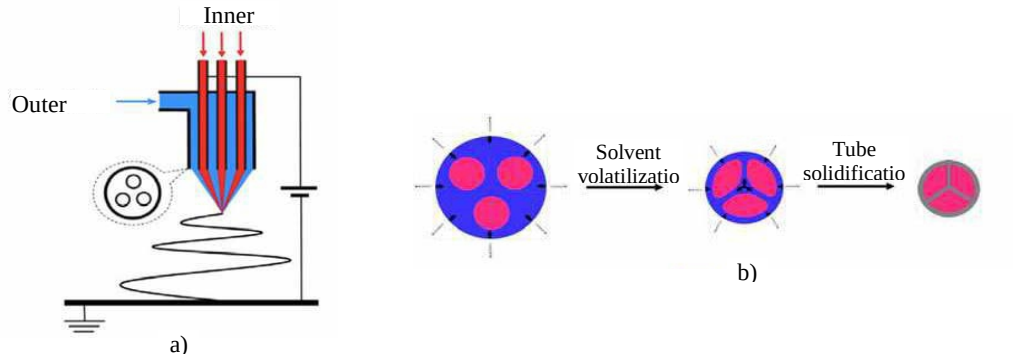

Fig.6: Schematic illustration of a) multi-channel coaxial electrospinning and b) fiber shaping

Wound dressing

Electrospinning can be applied to produce a scaffold with more homogeneity besides meeting other requirements like oxygen permeation and protection of wound from infection and dehydration for use as wound-dressing materials. Various types of synthetic and natural polymers like carboxyethyl chitosan/PVA (Khanam N et al. 2007), collagen/chitosan (Chen JP et al. 2008), silk fibroin, ABA type poly(dioxanoneco-L-lactide)-block-poly(ethylene glycol) block copolymer (Kim HY et al. 2004) have been electrospun to suggest them for wound-dressing applications. Further, wound-dressing material is produced by electrospinning as shown in figure 7 of PVA/$AgNO_3$ aqueous solution into non-woven webs and then treating the webs by heat or UV radiation (Hong KH et al. 2007)

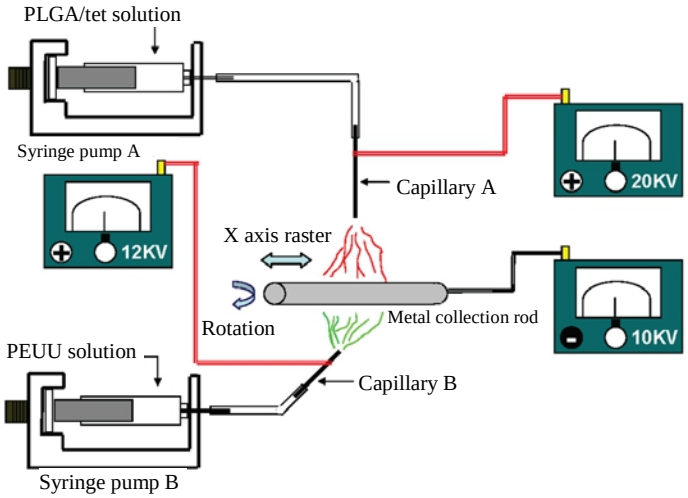

Fig.7: Two stream electrospinning (Hong Y et al. 2008)

Effects of various parameters on electrospinning.

The electrospinning process is affected by many parameters, classified broadly into polymer solution parameters, process parameters and ambient parameters. The parameters of polymer solution may be viscosity, conductivity, molecular weight, surface tension and process parameters include applied electric field, tip to collector distance and flow rate. Each of the parameters significantly affect the fibers morphology obtained as a result of electrospinning and by proper manipulation of these parameters, it is possible to get the nanofibers of desired morphology and diameters (Chong et al., 2007). Finally, ambient parameters encompass the humidity and temperature of the surroundings, which play a significant role in determining the morphology and diameter of electrospun nanofibers (Li and Xia, 2004).

Conclusion

Electrospinning is a very simple and versatile method for creating polymer based high functional and high performance nanofibers. Tthough, electrospinning is first described over 70 years ago, acceptability of the technique has increased dramatically in the past 10 years due to the rising interest in nanoscale properties of the materials. This technique allows for the production of polymer fibers with diameters on the nanometer scale.

Recently, electrospinning has gained popularity with the tissue engineering community as a potential means of producing scaffolds. The objective of this review is to describe briefly the theory behind the technique, observe the effect of changing the parameters on fiber morphology and discuss the application and impact of electrospinning on the field of tissue engineering. In the future it is important to apply this technique for the production of nanofibers from different types of polymers.

Electrospinning matrices are able to support the attachment and proliferation of a wide variety of cell types. Using innovative collectors and spinning techniques, scaffolds with aligned fibers, different compositions, improved mechanical properties, varying degradation rates or functional properties can be devedoped. Nevertheless, despite the comprehensive experimental and theoretical studies illustrating the ability to control fiber formation, concerns with fiber diameter uniformity still need to be addressed. In summary, electrospinning is an attractive and promising approach for the preparation of functional nanofibers due to its wide applicability to materials, low cost and high production rate.

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